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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/766,678	01/23/2001	Axel Ullrich	038602-1082	4384

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	PAPER NUMBER
1647	11

DATE MAILED: 11/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 8/26/02

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-46 is/are pending in the application.
Of the above, claim(s) 1-35, 43-46 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 36-42 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-46 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 9
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-421-632/40206

Part III: Detailed Office Action

Notice: **Effective June 18, 2000**, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1647**.

Restriction Requirement:

Applicant's election with traverse of Invention VIII, claims 36-43 in Paper No. 10 filed 8/29/02 is acknowledged. The traversal is on the ground(s) that examination of claims 36-43 would not present an undue search burden. This is not found persuasive because the argument is directed only to the elected Invention, and does not address any of the non-elected Inventions.

The requirement is still deemed proper and is therefore made FINAL.

Formal Matters:

The disclosure is objected to because of the following informalities: the status of the related applications to which reference is made at page 1§1 of the specification should be updated. Appropriate correction is required.

The Abstract of the Disclosure is objected to because it is two paragraphs long. The abstract should be only a single paragraph of 150 words or less. Correction is required. See M.P.E.P. § 608.01(b).

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim 43 is objected to because of the following informalities: the word "administrating" should read --administering--. Appropriate correction is required.

It is noted that the recitation in claims 40 and 41 of "cell line" is taken to indicate an *in vitro* cell population, and not to read on an animal or human.

Double Patenting Rejections:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36-41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5,851,999. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the patent cannot be practiced without infringing instant claims 36-39. Claims 40 and 41 differ from the patented claims in that they are drawn to cell lines comprising the vectors, and not the vectors themselves. However, they are not patentably distinct because It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make such cell lines for the purpose of producing retroviral particles for use in the pharmaceutical compositions of the patent, and also for propagation of the vectors.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because the meaning of "dominant-negative activity" is not clear and fails to particularly point out the subject matter which applicants regard as their invention. It is acknowledged that the Invention is drawn to t truncated forms of the receptor which are signaling-incompetent; however "dominant negative activity" does not convey this concept. It is noted that a soluble Flk-1 receptor which served to sequester all VEGF would be accurately described as having 'dominant-negative activity'. The term is further indefinite as applied to claim 42, which is drawn to an 'isolated' receptor protein with such activity; while the claim reads on membrane-bound forms, it also encompasses soluble forms of the protein: It is not clear how a soluble protein can be signaling competent, and by extension signaling incompetent; the concept of signaling does not apply to such forms.

Claim 43 is further indefinite as the preamble of the claim states "modulating", which can mean either a positive or negative effect, whereas the body of the claim merely states that the protein "inhibits" VEGF binding, thus achieving only one of the two possible goals set forth in the preamble. The preamble should be amended to be consistent with the rest of the claim.

The remaining claims are rejected for depending from an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. .

The specification does not enable an engineered cell line which produces infectious retrovirus particles "expressing truncated Flk-1". Rather, the specification enables an engineered cell line which produces infectious retrovirus particles which *encode* truncated Flk-1. The ordinary artisan would not know how to make a retrovirus *express* a protein, which term *express* is accepted in the art as indicating the process of transcription and translation wherein a particular protein is produced. As retroviral particles are incapable of transcription or translation, it would require undue experimentation to determine how to make such particles.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 102 prior to the amendment by the AIPA that forms the basis for the rejections under this section made in the attached Office action:

> **A person shall be entitled to a patent unless -**
>
> **(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.**

Claims 36, 38, and 40-42 are rejected under 35 U.S.C. §102(e) as being anticipated by Lemischka, U.S. Patent Number 5,185,438, cited by applicants. Lemischka discloses DNA encoding *flk-1* and vectors comprising such (see Figures 2a-2g). At column 6, it is indicated that the invention includes soluble forms of the flk-1 receptor, as well as vectors encoding such. Retroviral vectors are specifically mentioned at column 9 line 67. The Examiner notes that such soluble flk-1 would be expected to have a dominant negative

activity which would inhibit the cellular effects of VEGF binding by competitively inhibiting such binding.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36-42 are rejected under 35 U.S.C. § 103 as being unpatentable over Lemischka, U.S. Patent Number 5,185,438, Matthews et al. (PNAS 88:9026) and Terman et al. (BBRC 187:1579), in view of Ullrich et al. (Cell 61:203), and Ueno et al., (Science 252:844, Ueno-1 and JBC 267:1470, Ueno-2), all references cited by applicants.

Lemischka discloses DNA encoding *flk-1* and vectors comprising such (see Figures 2a-2g). At column 6, it is indicated that the invention includes soluble forms of the flk-1 receptor, as well as vectors encoding such. Retroviral vectors are specifically mentioned at

column 9 line 67.

Matthews et al. disclose a recombinant vector comprising cDNA which encodes Flk-1 (See Figure 1). In the abstract, Matthews et al. disclose that *Flk-1* has strong homology to the c-Kit subfamily of receptor kinases, and in particular to the *Flt* gene product.

Terman et al. (BBRC 187:1579) disclose cDNA encoding a receptor called KDR, and conclude on the basis of sequence similarity that KDR and Flk-1 are human and murine homologues of the same receptor, respectively (see page 1582, 2nd paragraph). Terman et al. further disclose that KDR encodes a receptor for VEGF, "an endothelial cell mitogen which stimulates angiogenesis" (see abstract). At page 1584, Terman et al. state that KDR is a type III receptor tyrosine kinase, and that the similarities between KDR and *flt*, another receptor, are "reminiscent of those between the α and β chains of the PDGF receptor." In the final paragraph, on page 1585, they conclude:

> "It will be of interest to determine whether there are further similarities between the VEGF and PDGF systems." They continue, "A recently discovered endothelial cell growth factor, PlGF is structurally related to VEGF in a manner reminiscent of the similarities between the A and B forms of PDGF. It is not known whether KDR and *flt* can form functionally active dimers analogous to the PDGF receptor dimers, αα, ββ and αβ. However, the existence of structural variants of growth factors and/or receptors may possibly explain multiple cellular responses to VEGF. For example, it is not known whether KDR, *flt*, or a heterodimer KDR/*flt* mediates mitogenic activity and/or vascular permeability."

Thus, the three primary references teach that Flk-1 is a VEGF receptor falling into the class of type III tyrosine kinase receptors, with strong homology to the c-Kit family of receptors. Also taught is the insertion of Flk-1-encoding DNA into vectors, including retroviral vectors. None of Lemischka, Matthews et al. or Terman teach or suggest construction of a recombinant vector encoding a truncated form of the disclosed *Flk-1* meeting the limitations of the claims (e.g. encoding amino acids 1-806 or other variant having extracellular and transmembrane domains but being signaling incompetent).

Ullrich et al. (Cell 61:203) disclose that "Receptor oligomerization is a universal

phenomenon among growth factor receptors" (page 203, second column). At page 206, Ullrich et al. discuss various experiments in which alterations were made to the protein kinase domain of receptors, including the deletion thereof. They state that "While the kinase activity of the various receptors was dispensable for their expression and targeting to the cell surface, it was indispensable for signal transduction and induction of both early and delayed cellular responses, including mitogenesis and transformation. Although normal in its binding characteristics, the kinase-negative mutant of the EGF receptor was unable to stimulate calcium influx, inositol phosphate formation, Na+/H+ exchange, ..." , continuing "This suggests that all receptor tyrosine kinase signaling activities depend on a functional tyrosine kinase...". Thus, Ullrich et al. disclose that an EGF receptor lacking a functional kinase domain was signaling incompetent.

The remaining cited references are all drawn to examples in which tyrosine kinase receptors structurally related to the Flk-1 receptor were altered within the cytoplasmic domain, resulting in proteins which formed signaling incompetent dimers, with dominant-negative characteristics.

Ueno-1 disclose PDGFβ receptor (a subclass III tyrosine kinase receptor) lacking most of its cytoplasmic domain (but retaining extracellular and transmembrane regions). The abstract of the article clearly states "a truncated receptor can inactivate wild-type receptor function by forming ligand-dependent receptor complexes (probably heterodimers) that are incapable of mediating the early steps of signal transduction." Although the exact nature of the truncation of the receptor was not disclosed, it is described at page 845, first column as lacking most of its cytoplasmic domain, but still being capable of binding PDGF. The concluding lines of the paper state "We have observed ligand-induced formation of inactive receptor complexes between wild-type receptor and mutant receptor. These complexes appear to be incapable of autophosphorylation and signal transduction."

Ueno-2 disclose a truncated form of Fibroblast Growth Factor Receptor 1 (FGFR) lacking most of its cytoplasmic domain formed complexes with wild type FGFR, consistent

with the hypothesis that the truncated FGFR interacted with wild type receptor to form nonfunctional heterodimers, thus eliminating the signaling by the wild-type FGFRs (see abstract). The truncated FGFR used by Ueno-2 consisted of the entire extracellular and transmembrane domains, and 8 amino acids of the cytoplasmic region (page 1471, first column). The final sentence of the paper suggests that inhibition of receptor function by co-expression of truncated FGFR can be used to block the actions of FGFR *in vivo*.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the nucleic acids and recombinant vectors of Matthews et al., Terman et al. or Lemischka to delete all or a portion of the sequence encoding the intracellular domain as taught by Ullrich and Ueno. The person of ordinary skill in the art would have been motivated to make such modifications in view of the teachings of Terman et al., specifically that Flk-1 is the murine homologue of the KDR receptor disclosed by Terman et al., and that it would be desirable to investigate the dimeric combinations in which the receptor occurs, and the relationship of such to the physiological responses known to occur in response to the ligand, VEGF (see teachings of Terman et al. as discussed above), and would further have been motivated by the teachings of Ullrich and Ueno that such deletions result in signaling incompetent receptors that act in a dominant-negative fashion *in vivo*, and that such results are expected to be generally applicable to tyrosine kinase receptors. The teachings of the secondary references would have provided further incentive to make such derivatives for the purpose of inhibiting the biological function of the receptor *in vivo*, which function was taught by Terman as being involved in angiogenesis. It would further have been obvious to incorporate such truncated coding sequences in a retroviral vector (and cell line containing such and producing infectious particles) because retroviral vectors are known in the art to be useful for the efficient vectors for the introduction of DNA into eukaryotic cells. With respect to the specific limitations in the claims as to termination of the coding sequence at the portion encoding amino acid 806, as this particular location falls within the cytoplasmic domain but results in the exclusion of the tyrosine kinase portion

of the molecule, it is deemed to be *prima facie* obvious especially in view of the teachings of Ullrich and Ueno that teach toward deleting the tyrosine kinase domain of the receptors.

Advisory Information:

Claim 43 is free of the cited prior art, and would be allowable if amended to overcome the objection and rejection under 35 U.S.C. § 112, second paragraph.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

Lorraine Spector

Lorraine Spector, Ph.D.
Primary Examiner